

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of determining whether an human individual has a predisposition to migraine comprising

obtaining a biological sample from said individual, said sample comprising at least one a first nucleic acid from said individual that comprises a nucleotide sequence of at least a fragment of a female steroid sex hormone receptor gene exon 8 of a human estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein; and

determining whether there is a polymorphism in said nucleotide sequence at said codon 594,

wherein the presence of the polymorphism in said nucleotide sequence indicates that said individual has an increased predisposition to migraine compared to an individual without the polymorphism.

2. (Canceled)

3. (Currently Amended) The method of Claim 21, wherein the polymorphism is a guanine to adenine change at nucleotide 2014 of the ESR1 gene.

4. (Currently Amended) The method of Claim 1, wherein said nucleotide sequence is of at least a fragment of a progesterone receptor gene, wherein said nucleotide sequence comprises a 306 base pair insertion in A method of determining whether a human individual has a predisposition to migraine comprising

obtaining a biological sample from said individual, said sample comprising at least a first nucleic acid from said individual that comprises a nucleotide sequence of at least a fragment of intron 7 of said a human progesterone receptor gene; and

determining whether there is a polymorphism in said nucleotide sequence, wherein the polymorphism comprises a 306 base pair insertion in intron 7,

wherein the presence of the polymorphism in said nucleotide sequence indicates that said individual has an increased predisposition to migraine compared to an individual without the polymorphism.

5. (Original) The method of Claim 3, wherein the polymorphism is detected as a restriction fragment length polymorphism.

6. (Original) The method of Claim 4, wherein said 306 base pair insertion is detected according to size.

7. (Currently Amended) The method of Claim 1, wherein said sample further comprises at least two nucleic acids from said individual, a first nucleic acid comprising a nucleotide sequence of at least a fragment of exon 8 of a human ESR1 gene and a second nucleic acid comprising a nucleotide sequence of at least a fragment of intron 7 of a human progesterone receptor gene.

8. (Original) The method of Claim 7, wherein the first nucleic acid comprises a polymorphism that is a guanine to adenine change at nucleotide 2014 of the human ESR1 gene and/or the second nucleic acid comprises a 306 base pair insertion in intron 7 of the human progesterone receptor gene.

9. (Currently Amended) A method of determining whether an human individual has a predisposition to migraine comprising

(a) obtaining a biological sample from said individual, said sample comprising

(i) a first nucleic acid that comprises a first nucleotide sequence of at least a fragment of a first female steroid sex hormone receptor gene exon 8 of a human estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein; and

(ii) a second nucleic acid that comprises a second nucleotide sequence of at least a fragment of a second female steroid sex hormone receptor gene intron 7 of a human progesterone receptor gene; and

(b) determining whether there is a polymorphism in each of said first and second nucleotide sequences, wherein the polymorphism in said first nucleotide sequence occurs at said codon 594, and the polymorphism in said second nucleotide sequence comprises a 306 base pair insertion in intron 7,

wherein the presence of at the polymorphism in said first nucleotide sequence of (i) and in said second nucleotide sequence of (ii) indicates that said individual has an increased predisposition to migraine compared to that of an individual having a polymorphism in said first nucleotide sequence(i) or said second nucleotide sequence(ii) alone.

10. (Canceled)

11. (Currently Amended) The method of Claim 109, wherein the polymorphism in said first nucleotide sequence is a guanine to adenine change at nucleotide 2014 of the ESR1 gene.

12. (Canceled)

13. (Currently Amended) The method of any of Claims 1, 4 or 9 preceding claim, wherein migraine is migraine with aura or migraine without aura.

14. (Currently Amended) The method of Claim 1, wherein the determining comprises amplifying said first nucleic acid with one or more primers for nucleic acid sequence amplification of said at least a fragment of ~~said female sex steroid hormone receptor gene exon 8 of a human estrogen receptor (ESR1) gene~~ that encodes codon 594 of an estrogen receptor protein.

15. (Canceled)

16. (Currently Amended) The method of Claim 1514, wherein the determining further comprises digesting amplification products with a *Btg1* restriction endonuclease.

17. (Currently Amended) The method of Claim 147, wherein the determining comprises amplifying said second nucleic acid with one or more primers ~~comprise~~ primers for nucleic acid sequence amplification of said at least a fragment of intron 7 of a human progesterone receptor gene.

18. (Currently Amended) The method of Claim 9, wherein the determining ~~comprising~~ comprises amplifying with one or more primers for nucleic acid sequence amplification of:

(i) the first nucleic acid that comprises the first nucleotide sequence of the at least a fragment of ~~the first female steroid sex hormone receptor gene exon 8 of a human estrogen receptor (ESR1) gene~~ that encodes codon 594 of an estrogen receptor protein; and

(ii) the second nucleic acid that comprises the second nucleotide sequence of the at least a fragment of ~~the second female steroid sex hormone receptor gene intron 7 of a human progesterone receptor gene~~.

19. (Canceled)

20. (Currently Amended) The method of Claim 1918, wherein the determining further comprises digesting amplification products with a *Btg1* restriction endonuclease.

21. (Withdrawn-Currently Amended) A method of determining whether an human individual has a predisposition to migraine comprising

isolating a progesterone receptor protein, or fragment thereof; and

determining whether said individual has a human progesterone receptor protein polymorphism comprising a 306 base pair insertion in the progesterone receptor gene,

wherein the presence of said polymorphism indicates an increased predisposition to migraine compared to an individual without the polymorphism.

22. (Canceled)

- 23. (Canceled)
- 24. (Original) The method of Claim 1, wherein the determining step comprises digesting said nucleic acid.
- 25. (Original) The method of Claim 1, wherein the determining step comprises gel electrophoresis of said nucleic acid.